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Prognostic factors in diffuse large B cell lymphoma: a retrospective analysis from a tertiary center

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ABSTRACT

Aims: This study aimed to evaluate the clinical characteristics and mortality risk factors of patients diagnosed with diffuse large B-cell lymphoma (DLBCL) in our center.

Methods: This cross-sectional study retrospectively analyzed the medical records of 74 DLBCL patients followed at the Hematology Clinic of Van Yüzüncü Yıl University between September 2016 and September 2021. Demographic characteristics, clinical findings, stage, treatments, and mortality-related risk factors were evaluated. Univariate and multivariable logistic regression analyses were performed to identify independent predictors of mortality.

Results: The median age of the patients was 54 years, and 59.5% were male. Of the patients, 29.7% resided in rural areas, and 66.2% were employed. The most common initial presentation was lymphadenopathy (56.8%), followed by B symptoms (43.2%). Regarding disease stage, 32.4% had stage III, 31.1% had stage IV, and 18.9% had bone marrow involvement. The mean International Prognostic Index (IPI) score was 2.07±1.67. R-CHOP was administered to 85.1% of patients, while 14.9% received R-EPOCH, and 5.4% were referred to other centers. Living in a rural area, unemployment, advanced age, presentation with B symptoms, stage IV disease, bone marrow involvement, triple hit lymphoma and higher IPI scores were significantly more common in 25 patients who died (33.8%) compared to 49 patients who survived (66.2%) ($p<0.05$). In multivariable logistic regression analysis, rural residency (OR: 93.706, 95% CI: 1.789–4908.115, $p=0.025$) and higher IPI scores (OR: 18.595, 95% CI: 2.761–125.236, $p=0.003$) were identified as independent risk factors for mortality in DLBCL patients.

Conclusion: This study demonstrated that rural residency and higher IPI scores are independent risk factors for mortality in DLBCL patients. Future multicenter prospective cohort studies with larger sample sizes and broader clinical parameters are needed to better define the risk factors associated with mortality in DLBCL.

Keywords: Lymphoma, large B-cell, diffuse, mortality, prognosis, rural population

INTRODUCTION

Large B-cell lymphomas represent a diverse array of disorders, comprising approximately 30–50% of all cases of non-Hodgkin lymphoma. Among these, DLBCL stands as the most prevalent variant, accounting for over 80% of reported instances.[1] Patients often present with progressive lymphadenopathy or extralymphatic manifestation, and the diagnosis is predominantly confirmed via excisional biopsy. DLBCL is further categorized into molecular subtypes, specifically the germinal center B-cell-like (GCB, 60%) and activated B-cell-like (ABC, 25–30%) classifications. The ABC subtype is linked to a less favorable prognosis and is more frequently encountered in older individuals and those exhibiting extranodal involvement.[1]

For the purposes of staging and evaluating therapeutic response in DLBCL, the Ann Arbor and Lugano classification systems are employed.[2-4] Positron emission tomography-computed tomography (PET-CT) is integral in assessing the overall tumor burden at the time of diagnosis and in monitoring treatment efficacy.[3] The conventional therapeutic strategy consists of immunochemotherapy regimens incorporating rituximab, with the R-CHOP regimen being

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the most widely adopted. Nevertheless, patients who exhibit primary or secondary resistance to treatment commonly face a grim prognosis.

The IPI is extensively utilized for prognostic assessment, and in recent years, innovative risk stratification frameworks that integrate biological and genetic markers have been established.[5-8] The etiology of DLBCL is complex and multifactorial, influenced by genetic susceptibility, viral pathogens, and environmental risk factors. Treatment modalities are tailored based on the patient's age, functional status, and the biological subtype of the malignancy.

This study seeks to explore the influence of both traditional prognostic indicators and social determinants, such as living in rural areas, on the prognosis of patients diagnosed with DLBCL, thus examining the correlation between living conditions and disease advancement.

METHODS

The research was sanctioned by the Van Yüzüncü Yıl University Hospital Scientific Researches Evaluation and Ethics Committee (Date: 10.12.2021, Decision No: 2021/13-19). Informed consent was obtained from all participants before the interventions. All procedures adhered to ethical standards and conformed to the principles set forth in the Declaration of Helsinki.

The sociodemographic attributes of the patients (age, gender, residence, occupation), characteristics pertinent to the disease (symptoms at presentation, stage at diagnosis, etiology, presence of genetic markers), IPI score, treatments administered, and clinical outcomes (mortality) were systematically assessed. The Ann Arbor classification was utilized for staging, whereas the IPI was applied for prognostic evaluation.[9,10]

Statistical Analysis

The data analysis was conducted using SPSS version 21.0. Categorical variables were reported as frequencies and percentages, while continuous numerical variables were represented as mean±standard deviation, or median (minimum–maximum) values. The Pearson's Chi-square test facilitated the comparison of categorical variables across groups. The normality of continuous numerical variables was evaluated through the Shapiro-Wilk test. Given that the normal distribution criterion was not satisfied, the Mann-Whitney U test was employed for comparisons between two independent cohorts. To ascertain independent risk factors for mortality, a multivariable logistic regression analysis (enter method) was executed, incorporating parameters that demonstrated statistical significance ($p<0.05$) in univariate assessments. The outcomes were summarized using odds ratios (OR) with 95% confidence intervals (CI). A bar graph was utilized to illustrate the distribution of categorical variables among groups. Statistical significance was established with a p-value <0.05.

RESULTS

In this investigation, a cohort of 74 individuals diagnosed with DLBCL was scrutinized, with a male representation of 59.5% (n: 44) and a mean age of 53.99±16.81 years. Notably, 29.7% of the participants were from rural locales, while 66.2% engaged in occupations yielding income. The predominant clinical manifestations included lymphadenopathy (56.8%) and B symptoms (43.2%). Within the patient population, 32.4% were categorized as stage III, 31.1% as stage IV, and 18.9% exhibited bone marrow infiltration. The average IPI score was recorded at 2.07±1.67. Genetic examinations disclosed double-hit mutations in 47.3% of the subjects and triple-hit mutations in 52.7% (Table 1). Pertaining to therapeutic interventions, 85.1% of the participants underwent R-CHOP treatment, in contrast to 14.9% who received R-EPOCH. During follow-up, it was observed that 33.8% of the individuals died and 66.2% survived. When the risk factors associated with mortality were evaluated, it was found that the patients who died were living in rural areas (60.0%-14.3%, $p<0.001$), unemployed (52.0%-24.5%, $p=0.018$), older age (mean 64.52±15.82%-48.61±14.73%, $p<0.001$), stage IV malignancy (64.0%-14.3%, $p<0.001$), showing bone marrow involvement (40.0% vs. 8.2%, $p=0.001$), having triple hit mutations (76.0% vs. 40.8%, $p=0.004$) and showing high IPI scores (28.0%, all patients with a score of 5 died) ($p<0.001$) (Table 2).

Table 1. Distribution of clinical characteristics of patients

Variables	n (%)
Gender	
Male	44 (59.5%)
Female	30 (40.5%)
Presenting complaint	
Lymphadenopathy	42 (56.8%)
B symptoms	32 (43.2%)
Stage (Ann Arbor)	
I	6 (8.1%)
II	21 (28.4%)
III	24 (32.4%)
IV	23 (31.1%)
Bone marrow involvement	
Absent	60 (81.1%)
Present	14 (18.9%)
Origin	
Germinal center	28 (37.8%)
Non-germinal center	46 (62.2%)
Genetic marker	
Double hit	35 (47.3%)
Triple hit	39 (52.7%)
IPI score	
0	18 (24.3%)
1	13 (17.6%)
2	15 (20.3%)
3	9 (12.2%)
4	12 (16.2%)
5	7 (9.5%)

IPI: International Prognostic Index

Through multivariable logistic regression analysis, residency in rural areas (OR: 93.706; 95% CI: 1.789–4908.115; $p=0.025$) and elevated IPI scores (OR: 18.595; 95% CI:

Table 2. Comparison of patients' clinical characteristics with mortality status

Variables	Exitus (n=25)	Alive (n=49)	p value
Initial complaint			
Lymphadenopathy	9 (36.0%)	33 (67.3%)	0.010
B symptoms	16 (64.0%)	16 (32.7%)	
Stage (Ann Arbor)			
I	0 (0.0%)	6 (12.2%)	<0.001
II	2 (8.0%)	19 (38.8%)	
III	7 (28.0%)	17 (34.7%)	
IV	16 (64.0%)	7 (14.3%)	
Bone marrow involvement			
No	15 (60.0%)	45 (91.8%)	0.001
Yes	10 (40.0%)	4 (8.2%)	
Origin			
Germinal center	6 (24.0%)	22 (44.9%)	0.080
Non-germinal center	19 (76.0%)	27 (55.1%)	
Genetic marker			
Double hit	6 (24.0%)	29 (59.2%)	0.004
Triple hit	19 (76.0%)	20 (40.8%)	
IPI score			
0	0 (0.0%)	18 (36.7%)	<0.001
1	0 (0.0%)	13 (26.5%)	
2	2 (8.0%)	13 (26.5%)	
3	6 (24.0%)	3 (6.1%)	
4	10 (40.0%)	2 (4.1%)	
5	7 (28.0%)	0 (0.0%)	

IPI: International Prognostic Index

2.761–125.236; p=0.003) were identified as independent risk factors contributing to mortality. The treatment modalities employed (R-CHOP and R-EPOCH) along with bone marrow transplantation did not exhibit a statistically significant effect on mortality (p>0.05). All independent risk factors that have an effect on mortality and risk factors that have no effect on mortality are listed in **Table 3**.

Table 3. Independent risk factors for mortality (multivariable logistic regression analysis, enter method)

Variables	OR [95% CI]	p value
Age	0.907 [0.803-1.024]	0.115
Residence (rural)	93.706 [1.789-4908.115]	0.025
Employment status	0.079 [0.004-1.614]	0.099
Chief complaint	2.704 [0.168-43.639]	0.483
Stage (Ann Arbor)	0.568 [0.095-3.389]	0.535
Bone marrow involvement	3.319 [0.095-115.819]	0.508
HIT	0.697 [0.068-7.166]	0.761
IPI score	18.595 [2.761-125.236]	0.003
Constant	3.369	0.787

OR: Odds ratios, CI: Confidence interval, IPI: International Prognostic Index Dependent variable: Mortality status; Nagelkerke R^2: 0.848

DISCUSSION

DLBCL is the most common subtype of non-Hodgkin lymphoma, and its prognosis varies depending on clinical and biological factors. Response rates to the standard R-CHOP regimen range between 50% and 80%, while 20% to 50% of patients experience resistance or relapse.[11] Therefore, early prognostic assessment of the disease is of great importance.

In this study, the mortality rate among DLBCL cases was determined to be 33.8%, which is consistent with previously reported mortality data. Based on disease extent, five-year survival rates have been reported to range between 57% and 74%.[12] The relatively short follow-up period in our study made it challenging to determine a definitive survival rate. Regarding the epidemiological characteristics of the disease, 59.5% of the patients were male. Previous studies have also reported that DLBCL is more frequently observed in males.[13,14] However, no significant association between gender and mortality was identified in our study.

The mean age at diagnosis was calculated as 54 years, which is relatively lower compared to previous studies.[15] Although the patients who died were older, age was not found to be an independent risk factor for mortality. An increase in IPI score was determined to significantly elevate the risk of mortality, independent of other variables (OR: 18.595; 95% CI: 2.761–125.236, p=0.003). Consistent with previous studies, higher IPI scores were confirmed to be associated with lower survival rates.[16]

Regarding the clinical presentation of the disease, the most common presenting symptoms were lymphadenopathy (56.8%) and B symptoms (43.2%). Although B symptoms are more common in dying patients, they have not been identified as an independent risk factor for mortality. Stage IV disease and bone marrow involvement were observed more frequently in patients who died; however, similar to the findings in other studies, these parameters were not independent risk factors for mortality.[17]

In our study, compared to those residing in urban areas, individuals living in rural regions exhibited a significantly higher risk of mortality (OR: 93.706 [95% CI: 1.789–4908.115], p=0.025). Previous studies have investigated the impact of residential areas on DLBCL outcomes. Tao et al.[18] conducted a study evaluating the effect of socioeconomic status on mortality in DLBCL patients and reported that individuals living in neighborhoods with lower socioeconomic levels had significantly poorer survival outcomes following a DLBCL diagnosis. The study highlighted that one of the most critical indicators of this association was whether patients resided in urban or rural areas, emphasizing that those living in rural regions were often surrounded by communities with similarly lower socioeconomic status.[18]

Similarly, Loberiza et al.[19] found that compared to lymphoma patients residing in rural areas, those living in urban regions had a significantly lower risk of mortality. Conversely, Lee et al.[20] reported that DLBCL patients in rural areas exhibited survival rates comparable to those in major urban centers and central regions, whereas patients residing in small to medium-sized urban areas had poorer outcomes.

Several studies have attempted to explain the potential causes of this phenomenon, suggesting that cancer patients in urban areas have better access to healthcare services compared

to those in rural regions. This improved access is believed to positively influence survival duration and survival probability.[21-24] In our study, we also hypothesize that the increased mortality rate among patients living in rural areas may be associated with poorer access to healthcare services and lower health awareness within this population.

Limitations

The major limitations of this study include the short follow-up period, single-center nature, and lack of direct measurement of socioeconomic status and access to healthcare. Additionally, additional factors such as treatment response and toxicity were not assessed in detail.

CONCLUSION

In this study, clinical and epidemiological factors associated with mortality in DLBCL patients were evaluated. High IPI score and residence in rural areas were identified as independent prognostic risk factors. Mortality rates were consistent with previously reported data in the literature, with factors such as advanced disease stage, bone marrow involvement, and triple-hit mutation being significantly associated with mortality. However, gender, treatment regimen, and bone marrow transplantation did not demonstrate a significant impact on overall survival. This study demonstrates the need for multicenter studies that include treatment-related variables in order to better evaluate treatment responses and prognosis.

ETHICAL DECLARATIONS

Ethics Committee Approval

The research was sanctioned by the Van Yüzüncü Yıl University Hospital Scientific Researches Evaluation and Ethics Committee (Date: 10.12.2021, Decision No: 2021/13-19).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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